Remarks

Claims 35, 46, 54 and 86-87 are amended herein to incorporate the limitations of claims 75 and 79. Additional support for the amendments to claims 35, 46-47 and 54 can be found throughout the specification, such as, but not limited to, at page 31 and pages 33-35. Claims 86-87 are amended to correct form. Claims 75 and 79 are canceled herein. Reconsideration of the application is respectfully requested in view of the foregoing amendments and following remarks.

Applicants believe no new matter is added herein. Applicants believe that the application will be in condition for allowance following entry of this amendment.

Claim Rejections Under 35 U.S.C. 112, first paragraph

Claims 35, 46, 47, 54 and 60-77 and 87 are rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the written description requirement. Applicants respectfully disagree with this rejection as applied to the claims as amended.

Claims 35, 46 and 54 are amended to incorporate the limitations of claims 75 and 79, in order to expedite allowance. It is noted that claims 77 and 79 were not included in the present rejection. Applicants expressly reserve the right to Appeal the re-asserted rejection. Claims 54, 60-77 and 87 depend therefrom. The rejection is addressed as it might be applied to the claims as amended.

MPEP § 2163 clearly sets forth that:

> '[t]o satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See, e.g., *Moba, B.V. v. Diamond Automation, Inc.*, 325 F.3d 1306, 1319, 66 USPQ2d 1429, 1438 (Fed. Cir. 2003); *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116....An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was

> complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406; *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it")." [emphasis added]

At the outset the following facts are noted:

1. The nucleic acid sequences, SEQ ID NO: 1, SEQ ID NO: 14, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 21 are provided in the specification (see the specification at pages 19-24 and the sequence listing).
2. A description of the critical features of the claimed nucleic acid used, namely that they comprise from 2 to 4 guanosine-rich sequences and form a G-tetrad, and have a circular dichromatism (CD) value of greater than 2.9 (a property inherent to oligodeoxynucleotides comprising SEQ ID NO: 1, SEQ ID NO: 14, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 21) is provided in the specification (see pages 19-29).
3. A working example, documenting that an oligonucleotide that comprises SEQ ID NO: 1 reduces tumor necrosis fact (TNF)α, macrophage inflammatory protein (MIP)-2, interleukin (IL)-6 and keratinocyte-derived chemokine (KC) (see the specification, pages 32-36).
4. Post-filing date evidence was submitting documenting ODNs that comprise from 2 to 4 guanosine-rich sequences and form a G-tetrad, and have a circular dichromatism (CD) value of greater than 2.9 and reduce cytokine production. Specifically, evidence was submitted on September 3, 2008 documenting that seven of the exact nucleic acid sequences described in the specification (SEQ ID NO: 1, 2, 3, 4, 7, 12, and 20) had the immunsuppressive effects.

The Office action alleges that "[t]o adequately describe a genus of suppressive oligodeoxynucleotides (SEQ ID NO: 14, SEQ ID NO: 17 SEQ ID NO: 18, SEQ ID NO: 19 SEQ ID NO: 21) or a combination of two or more suppressive oligodeoxynucleotides thereof (SEQ ID NO: 1, SEQ ID NO: 14, SEQ ID NO: 17 SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 21), applicant must adequately [sic] which specific ODNs, if any, have efficacy in thereby reducing the production of a given cytokine or chemokine in the subject and reducing the production of a cytokine or chemokine in a cell in vitro" (see page 5). The Office action acknowledges that results are presented documenting that SEQ ID NO: 1 reduces the production of tumor necrosis factor (TNF)α, macrophage inflammatory protein (MIP)-2, interleukin (IL)-6 and keratinocyte-derived cytokine (KC), and acknowledges that there is a description of ODNs of 22-30 nucleotides that have specific features (see pages 5-6). The Office action also acknowledges that the specification defines suppressive ODNs capable of forming G-tetrads that can suppress immune activation (see page 5). However, the Office action alleges that there is not an adequate description of the claimed genus of ODNs because "the specification does not provide guidance as to how to distinguish which ODNs are specifically suppressive....Applicants have not demonstrated that any examples aforementioned above are representative of a genus of oligonucleotides excluding SEQ ID NO: 1 or a combination including SEQ ID NO: 1 for the recited methods as claimed...Applicant has not demonstrated that suppressive oligodeoxynucletodies or a combination of two or more thereof aforementioned above with a length between 22-30 nucleotides as stated in dependent claim 70 posses the abilities of reducing the production of a cytokine or chemokine in the subject and reducing the production of a cytokine or chemokine in a cell *in vitro*." Applicants respectfully disagree.

The MPEP acknowledges that possession of a claimed invention, such as the presently claimed methods, can be shown in many ways. Specifically, MPEP § 2163 states:

> "...[p]ossession may also be shown by a clear depiction of the invention in detailed drawings or in structural chemical formulas which permit a person skilled in the art to clearly recognize that applicant had possession of the claimed invention. An adequate written description of the invention may be shown by any description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention. See, e.g., *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1323, 56 USPQ2d 1481, 1483 (Fed. Cir. 2000) (the written description "inquiry is a factual one and must be assessed on a case-by-case basis"); see also *Pfaff v. Wells Electronics, Inc.*, 55 U.S. at 66, 119 S.Ct. at 311, 48 USPQ2d at 1646.... An applicant may show possession of an invention by disclosure of drawings or structural chemical formulas....*Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406 ("In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that

> the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus."). An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. *Enzo Biochem*, 323 F.3d at 964, 63 USPQ2d at 1613." [emphasis added]

MPEP § 2163 specifically addresses biomolecules:

> "For some biomolecules, examples of identifying characteristics include a sequence, structure, binding affinity, binding specificity, molecular weight, and length. Although structural formulas provide a convenient method of demonstrating possession of specific molecules, other identifying characteristics or combinations of characteristics may demonstrate the requisite possession. [emphasis added]

Thus, the factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406. The Office action at pages 6-7 provides a reference to the relevant section of the MPEP.

In the present case, the specification clearly provides the structure (the nucleic acid sequence set forth as SEQ ID NO: 1, SEQ ID NO: 14, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 21), physical and chemical properties (the ODN include from 2 to 4 guanosine-rich sequences and form a G-tetrad, and have a circular dichromatism (CD) value of greater than 2.9) and provides a function (the reduction of cytokine production), and a length (10 to 30 nucleotides). There is complete description of a reduction in cytokine production, and methods to measure this reduction (see, for example, Examples 1-3 presented in the specification on pages 32-24). As noted in the Office action, there also is evidence of reduction to practice in the specification, specifically SEQ ID NO: 1 was demonstrated to reduce the expression of

TNFα, MIP-2, IL6 and KC. There has also been post-filing date evidence presented documenting that other ODNs with the same structural features (comprise from 2 to 4 guanosine-rich sequences and form a G-tetrad, and have a circular dichromatism (CD) value of greater than 2.9 and reduce cytokine production) have immunosuppressive effects. Thus, there is clear written description for the presently claimed methods.

The Office action acknowledges that Examples 1, 2, and 3 teach exemplary methods of reducing cytokine production and chemokine using an exemplary ODN (SEQ ID NO: 1). However, the Office action appears to require that experimental evidence be presented in the specification documenting that all of SEQ ID NO: 14, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, and SEQ ID NO: 21 reduce cytokine expression. There is no precedent to require actual experimental data obtained with each species of a generic invention in order to comply with a written description requirement. MPEP § 2163 states:

> As explained by the Federal Circuit, "(1) examples are not necessary to support the adequacy of a written description; (2) the written description standard may be met even where actual reduction to practice of an invention is absent; and (3) there is no per se rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure." *Falkner v. Inglis*, 448 F.3d 1357, 1366, 79 USPQ2d 1001, 1007 (Fed. Cir. 2006)."

Thus, it is clear that an actual reduction to practice of each of SEQ ID NO: 14, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, and SEQ ID NO: 21 in the specification is not required to meet the written description requirement.

The Office action acknowledges that results are presented in the specification using one model system of inflammation. This model system uses CpG ODNs to induce inflammation. In view of the use of this model system, the Office action alleges that there is only sufficient written description for reducing cytokine expression that is induced by CpG ODN. Once again, this is an improper standard. MPEP § 2163.02 clearly states that the written description requirement is met if the description clearly allows one of ordinary skill in the art to recognize the claimed invention. In the present application, one of skill in the art would readily understand that ODNs of 10-30 nucleotides in length that comprise SEQ ID NO: 14, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, and SEQ ID NO: 21, could be used to reduce cytokine expression that results from inflammation from any source.

It is difficult to determine why it is asserted in the Office action that there is insufficient written description for one of skill in the art to reduce cytokine expression resulting from any type of immune response. There simply is *no scientific rationale* provided in the Office action for this assertion. The Applicants clearly describe many types of inflammation wherein cytokine expression can be reduced (see pages 28-32). Methods of measuring cytokine levels in body fluids are known in the art, including the use of cell culture supernatents and ELISA assays (see the specification at page 31, lines 16-26). Exemplary results are provided in a model system of (CpG induced inflammation), which demonstrates reduction to practice. Thus, there is clear descriptive support for the use of the claimed ODNs to decrease cytokine expression.

The Office action appears to allege that a reduction in cytokine expression is specific to the agent that initiates cytokine expression, and thus asserts that there is written description only for the reduction of cytokine expression in response to immunostimulatory (CpG ODN), since this is the reduction to practice presented in the examples section. However, of skill in the art understands that a compound that reduces cytokine expression will work regardless of the initiating event. As an example, one of skill in the art understands that a non-steroidal anti-inflammatory agent such as ibuprofen can treat a headache pain, regardless whether the headache was caused by a strobe light, muscle tension, stress or a viral infection. Similarly, one of skill in the art understands that a cyclooxygenase (Cox) inhibitor works for the treatment of inflammatory arthropathy and reduces cytokine expression, regardless of whether arthritis is induced by an autoimmune process, collagen or CpG oligodeoxynucleotides. One of skill in the art understands that interferon-beta or daclizumab have been proven to be clinically effective for the treatment of multiple sclerosis, even though the causative agent for this disease is unknown. The disclosure provided in the specification that describes the reduction in cytokine expression is sufficient for one of skill in the art to understand that the cytokine expression can be reduced by inhibiting a biological pathway, regardless of the initiating event.

There clearly is sufficient written description for the amended claims. Reconsideration and withdrawal of the rejection are respectfully requested.

Claims 35, 46, 47, 54 and 60-87 are rejected under 35 U.S.C. 112, first paragraph, as allegedly not being enabled by the specification. Claims 75 and 79 are canceled herein, rendering the rejection moot as applied to these claims. The Office action alleges that the specification is enabling only for methods of reducing the production of TNFα, MIP-2, IL-6 and KC induced by oligodeoxynucleotides (ODNs) by administering an ODN consisting of SEQ ID NO: 1. Applicants respectfully disagree with this rejection as applied to the claims 35, 46-47, 54 and 60-74 and 80-87 as amended.

At the outset, it is important to note that claim 78 is directed to the use of an ODN that "consists of" SEQ ID NO: 1, which is acknowledged to be enabled on page 7 of the Office action. Thus, Applicants believe that this claim was included in the rejection in error. The rejection is addressed below for claims 35, 46-47, 54, 60-77 and 80-87.

Applicants assert that the specification enables one of skill in the art to make and use the invention of the amended claims without undue experimentation. A Wands analysis is provided below:

(A) *Breadth of claims:* The amended claims are limited to methods of reducing four cytokines (TNFα, MIP-2, IL-6 and KC) using suppressive ODNs that comprise the sequences of SEQ ID NO: 1 (claim 35), SEQ ID NO: 14, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 21, or a combination of two or more thereof (claim 46 and 54). These ODNs are at most 30 nucleotides in length, and have two to four guanonsine rich sequences and form a G-tetrad. Claims 60, 70-74 and 78 are limited to methods for reducing the expression of TNFα, MIP-2, IL-6 and KC wherein the ODN consists of SEQ ID NO: 1, SEQ ID NO: 14, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, or SEQ ID NO: 21. Thus, the methods are limited to reducing ODNs have a specified sequence, length and physical characteristics. The claims are narrow in scope.

(B) Nature of the invention: The claims are directed to methods of treatment that utilize nucleic acid sequences with a very specific sequence (SEQ ID NO: 1, SEQ ID NO: 14, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, or SEQ ID NO: 21), length (up to 30 nucleotides) and physical characteristics, to reduce expression of four specific cytokines, namely TNFα, MIP-2, IL-6 and KC.

(C) State of the prior art: The U.S. Patent and Trademark Office (PTO) has previously acknowledged that synthesis of ODNs, administration of ODNs to a subject of interest, and art-recognized models for testing therapies are well known in the art (see the Office action dated May 16, 2008). In addition, methods for measuring TNFα, MIP-2, IL-6 and KC are well known in the art; kits to measure these cytokines are commercially available.

(D) Level of ordinary skill in the art: The U.S PTO has previously acknowledged that the level of ordinary skill in the art is of a molecular biologist and/or pulmonologist is high (see the Office action dated May 16, 2008). Applicants assert that given the disclosed ODN sequences, one of skill in the art could readily make and use the claimed invention.

(E) Level of predictability in the art: Production of ODNs comprising the sequences set a specified nucleic acid sequence, and of a specified length is routine in the art. Further, there are methods, such as ELISAs (or ELISPOT) that are commercially available that can be used to measure cytokine production. The Office has acknowledged that there are art recognized models for inflammatory lung disease that can be used to test the effects of the ODNs of interest *in vivo*. These are also described in the specification. Exemplary results documenting the reduction in cytokine expression are also provided in the specification (see, for example, pages 34-35).

(F) Amount of direction provided: The specification provides the sequences of the ODNs for use in the claimed methods (for example, Table 1, page 22). The specification further provides pharmaceutical compositions and methods of administration of ODNs (for example, page 24, line 9 to page 30, line 10) and methods for determining the effectiveness of an ODN, including methods for measuring cytokine or chemokine production (for example, page 30, line 11 to page 31, line 26; page 32, line 25 to page 34, line 16).

(G) Working examples: The specification provides the sequences of ODNs for use in the claimed methods and provides the use of an exemplary ODN (SEQ ID NO: 1) in inhibiting cytokine production *in vitro* (Example 2) and in an animal model of inflammation (Example 3).

The Office action alleges that the use of only one ODN (SEQ ID NO: 1) in the working examples is evidence that the full scope of the claims is not enabled by the sepcification. However, MPEP § 2164.02 clearly states that, "one must evaluate all the facts and evidence and state why one would not expect to extrapolate that one example across the entire scope of the claims." The specification provides suppressive ODNs of SEQ ID NO: 1, SEQ ID NO: 14, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19 and SEQ ID NO: 21and describes characteristics of ODNs that are useful in the claimed methods, namely that they (1) are 10-30 nucleotides in length, (2) have a CD value of greater than about 2.9 (for example, see the specification on page 20, lines 15-24), and (3) form a G-tetrad (for example, see the specification on page 20, lines 7-14). One of skill in the art would expect that ODNs comprising the sequences of SEQ ID NO: 1, SEQ ID NO: 14, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, or SEQ ID NO: 21would be effective to reduce expression of TNFα, MIP-2, IL-6 and KC, based on the teachings in the specification, as well as the experimental evidence provided for SEQ ID NO: 1.

Furthermore the Applicants have provided substantial evidence documenting showing that other ODNs from the group of sequences of SEQ ID NOs: 2-25 have subsequently been shown to be useful in reducing the production of cytokines. For example, Yamada *et al.* (*J. Immunol.* 169:5590-5594, 2002; of record) shows that suppressive ODNs H154 and 1502 (Table 1, SEQ ID NOs: 1 and 20, respectively) inhibit production of Il-6, IL-12 and interferon-gamma (see *e.g.* Figures 1, 2 and 4, page 5591). Further, Gursel *et al.* (*J. Immunol.* 171:1393-1400, 2003; submitted previously) show that ODNs having the sequences of SEQ ID NOs: 1, 2, 3, 4, 7, and 12 suppress cytokine production in BALB/c spleen cells (see *e.g.*, Figure 3A (SEQ ID NOs: 2, 3, 4, and 7) and Figure 3D (SEQ ID NOs: 1 and 12), page 1396). In addition, *in vivo* administration of the suppressive ODN of SEQ ID NO: 2 inhibited cytokine production in mice (Gursel *et al.* Figure 5, page 1398). Finally, Shirota *et al.* (*J. Immunol.* 174:4579-4583, 2005; submitted previously) teach that suppressive ODN A151 (SEQ ID NO: 2) inhibits IFN-γ production in BLAB/c mice treated with LPS (see *e.g.*, Figure 5A, page 4581). Thus, ODNs disclosed in the specification were shown to inhibit cytokine expression induced by either CpG and LPS. These examples clearly show that the ODNs disclosed in the specification can be used in the claimed methods.

Moreover, submitted herewith is the Declaration of Dr. Gursel. This Declaration describes results achieved using the ODNs and the methods disclosed in the specification. Dr.

Gursel tested the effect of ODNs comprising SEQ ID NO: 14, 17, 18, 19 and 21 to suppress cytokine production. ODNs comprising the nucleic acid sequence set forth as SEQ ID NO: 14, 17, 18, 19 and 21 reduced expression of TNF-α, IL-6, MIP-1a and MIP-3a. Although Dr. Gursel did not specifically examine the production of MIP-2 or KC, the Declaration provides a scientific explanation and citations that support the assertion that one of skill in the art would also accept that the production of these cytokines should also be reduced.

This Declaration provides evidence that the specification is fully enabling for the claimed methods. In fact, nucleic acid molecules including SEQ ID NO: 1, 14, 17, 18, 19 and 21 have been tested and demonstrated to reduce ctyokine expression, using exactly the methods described in the specification.

Thus, it has been documented that the presently claimed methods not only are fully enabled by the specification, but have been reduced to practice. Reconsideration and withdrawal of the rejection are respectfully requested.

(H) Experimentation needed: Applicants assert that given that the amended claims are limited to the ODNs comprising SEQ ID NO: 1, 14, 17, 18, 19 and 21, it would require only routine experimentation for one of skill in the art to formulate the ODNs for use in the described methods to assess effectiveness of an ODN (for example, see page 30, line 11 to page 31, line 26). This limited experimentation and the predictable results are also demonstrated in the Declaration of Dr. Gursel, submitted herewith.

Based on the foregoing arguments, it would not require undue experimentation for one of skill in the art to make and use the claimed invention. Therefore, Applicants assert that the claims as amended are enabled by the specification and respectfully request withdrawal of this rejection under 35 U.S.C. § 112, first paragraph.

Conclusion

Applicants have made every effort to place the present application in condition for allowance. In the unlikely event that anything further is required before the allowance of all of the pending claims, Examiner Archie is formally requested to contact the undersigned prior to issuance of the next Office action, in order to arrange a telephonic interview with the supervisory Examiner present. It is believed that a brief discussion of the merits of the present application may expedite prosecution. This request is being submitted under MPEP §713.01, which indicates that an interview may be arranged in advance by a written request.

Respectfully submitted,

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